Translational Research in Dementia
NOCRI simplifies access to the UK’s world-leading clinical research infrastructure in Dementia through the NIHR Translational Research Collaboration
Foreword

Dementia is a growing global problem that is affecting millions of people. Dementia profoundly affects the lives of sufferers and also those of their families and carers. The scale of the problem brings significant costs to health and social care systems, and has major economic impacts.

This is why the Prime Minister launched his challenge on dementia, which aims to deliver major improvements in dementia care and research by 2015.

Since 2006, in the UK the Government has fostered the development of a unique health research system, the National Institute for Health Research (NIHR). This builds on the country’s excellence in science within our world-class universities, and on the power of the National Health Service to deliver world-class research.

In direct response to the call for improved research in dementia, the new NIHR Dementia Translational Research Collaboration is bringing the nation’s world-class dementia researchers together for the benefit of patients, the NHS, universities, and partner research funders. This Collaboration has a specific goal to deliver high quality collaborative research with industry.

This booklet introduces the Collaboration and outlines some of the many capabilities hosted within it.

I invite the life sciences industry to engage with the NIHR Dementia Translational Research Collaboration and all our research, and to work together on the development of new approaches to tackle the global problem of dementia.

Professor Dame Sally C Davies
Chief Medical Officer and Chief Scientific Adviser, Department of Health
Dementia today

Government support

In March 2012 the Prime Minister identified three key areas where the UK Government aims to make a difference in this global cause:

• Making sure health and social care systems are properly geared up to deal with the crisis
• Radically stepping up research into cures and treatments, with overall funding for dementia research doubled to reach £66m by 2015
• Getting society involved in the challenge: communities, charities, businesses.

The ‘dementia challenge’ in numbers

• Globally, there are an estimated 40m people suffering with dementia. The majority of the projected growth in this figure will come from the fast growing elderly populations in China and India
• There are an estimated 670,000 people in England with dementia and numbers are expected to double within thirty years
• Just 42 percent of people with dementia have been diagnosed. This means around 400,000 people do not know they are living with the condition
• A 2011 YouGov poll showed that 39 percent of over 55s most feared getting Alzheimer’s disease, as compared to 25 percent who most feared getting cancer
• The Dementia UK report (2007) estimated that dementia costs society £17bn per year and this has now risen to £23bn for the UK and £19bn for England.

Overall funding for dementia research doubled to reach £66m by 2015
The NIHR Dementia Translational Research Collaboration

Dementia research is characterised by considerable methodological and disciplinary diversity. Effectively addressing the main research questions will require drawing on a wide range of scientific areas and specialist expertise from around the world. Collaboration between disciplines, specialities and sectors will be vital to progress.

To help meet the challenge, the UK government has established the new National Institute for Health Research (NIHR) Dementia Translational Research Collaboration (TRC) to pull discoveries from basic science into real benefits for patients. The Collaboration comprises four new NIHR Dementia Biomedical Research Units as well as six NIHR Biomedical Research Centres with dementia-related research themes. These Units and Centres are world leaders in translational research, based within top university-NHS partnerships. The Collaboration is a new and important part of the NIHR clinical research infrastructure and offers a unique opportunity to maximise the significant NIHR investment in dementia translational research.

As with all areas of unmet patient need, industry plays a crucial role in the development of new interventions to tackle dementia. Better collaboration between academia, the NHS and industry, with greater mutual transparency is vital. The opportunity for such collaboration has never been greater given global biopharma is opening up its development programmes to collaboration to access innovative new approaches to research and development.

The NIHR Office for Clinical Research Infrastructure (NOCRI) provides streamlined and coordinated access to the Collaboration for life science industry partners. For information visit www.nihr.ac.uk/nocri.
Partnership with industry is a major focus for the NIHR Dementia Translational Research Collaboration. The NIHR Dementia Biomedical Research Units and the NIHR Biomedical Research Centres which make up the collaboration will work closely together on questions of early diagnosis, patient stratification, phase I and phase II experimental medicine and proof of concept trials. These activities are underpinned by expertise in biomarker discovery, validation and qualification and platforms for research including large patient populations, biobanks and other bioresources and facilities for complex studies.

**How NOCRI can help**

NOCRI is a unique resource for the global life sciences industry – improving the quality, efficiency and success of translational research. NOCRI enable this by providing:

- fast and easy access to the NIHR Dementia TRC and other NIHR-funded research infrastructure in the NHS
- rapid connection to the most relevant expert investigators and cutting edge technologies
- a managed process for collaborative research.

**NIHR support for industry**
Connecting to later phase work and wider patient populations

Beyond the world leaders in translational research that make up the Dementia Translational Research Collaboration, the NIHR has established a Clinical Research Network to support later phase clinical research throughout the NHS. The NIHR Dementias and Neurodegenerative Diseases Research Network (DeNDRoN) provides a dedicated, trained workforce to improve feasibility assessment, site selection, set up and delivery of clinical research in dementia.

Through NOCRI, DeNDRoN can provide access to a wider clinical research infrastructure that can increase:

- the scope of translational research at TRC centres by recruiting patients from surrounding clinical services
- the pull through from early to later phase research by providing a single point of access to NHS clinical research centres
- the opportunities for conducting translational research by nesting experimental studies within later phase trials.

Strengths and expertise

Together the NIHR Dementia Translational Research Collaboration offers world-leading expertise in:

- Late-onset dementias, including Alzheimer’s Disease, Vascular Disease and Lewy body dementia
- Young-onset dementias
- Frontotemporal dementia with motor neuron disease
- Parkinson’s Disease, including progression to dementia
- Neuroinflammation
- Huntington’s Disease.

The NIHR Dementia Translational Research Collaboration offers internationally recognised strengths in:

- Patient stratification through identification and validation of diagnostic and prognostic biomarkers of disease and genetic markers of susceptibility
- Discovery, development and delivery of innovative disease modifying therapies, which include those discovered through the longitudinal study of genetically at-risk cohorts
- Identification of new disease-causing genes and subsequent development of clinical testing
- Extrapolation of discoveries in young onset dementia to older patient groups
- Detection, prevention and treatment of protein misfolding and aggregation in dementia.
1. Infrastructure

Dedicated, purpose built, Clinical Research Facilities with expertise in dementia and cognition research.

Centre for Innovative Manufacturing in Emergent Macromolecular Therapies – this Engineering and Physical Sciences Research Council (EPSRC) Centre aims to greatly reduce the time and cost of developing new treatments as well as improving access to drugs with advanced therapeutic properties.

Cell and gene-based therapies - Good Manufacturing Process (GMP) resources for stem cells and regenerative medicine plus gene therapy consortia: world class collection of investigators centred around viral vector production facilities, supported by Advanced Therapies Regulatory Managers to speed up clinical trial approvals.

Genomics including sequencing techniques for identification of new disease genes.

Imaging - world class capabilities including:

• Imaging biomarkers for research and development
• GMP radiochemistry facilities accredited to produce radiotracers
• Extensive portfolio of GMP Positron Emission Tomography (PET) neuro-radiopharmaceuticals, including markers for amyloid, neuroinflammation, blood flow and metabolism
• The latest clinical scanners from: GE, Siemens, and Philips
• Scanners to study disease models
• Expertise in design, set-up, quality control and analysis of imaging data for multi-centre trials.

Informatics with expertise and capabilities combining statisticians, sequencing technologies, bioinformaticians, clinical informaticians and epidemiologists. Capacity for integrating biological and clinical datasets and in complex statistics for biomarker discovery and risk evaluation.
2. Tissue

Biobanks and Brain Banks
- Biobanks holding thousands of control and disease tissue samples
- Brainbanks that support consent, donation, diagnostic neuropathology and long term storage for neuropathological tissue based projects and population based neuropathology
- Brain tissue with outstanding collections of post-mortem tissue from clinically and neuropathologically well-characterised cases of late-onset dementia in addition to other neuropsychiatric and neurodegenerative disorders
- The Medical Research Council-led UK Brain Banks Network
- The Alzheimer's Research UK and Alzheimer's Society ‘Brains for Dementia Research’ initiative, a UK-wide collaboration in brain banking that provides samples including plasma, serum, urine, DNA and RNA managed through a central coordinating centre.

3. Patients

Electronic Medical Records with appropriate safeguards for consent and confidentiality for use in research for: care pathway mapping, risk evaluation and aides to decision making, trials feasibility studies and for recruitment to clinical research including interventional trials.

Patient Recruitment support through DeNDRoN, a national resource allowing local access to recruitment from representative clinical populations of those with different types of dementia and other neurodegenerative diseases.

Cohorts and registries
- Alzheimer’s Disease (AD) including young-onset, posterior variant of AD, familial AD including at risk premanifest mutation carriers
- Lewy body dementia
- Early dementias including primary tauopathy such as progressive supranuclear palsy
- Frontotemporal lobar degeneration including at risk premanifest mutation carriers
- Huntington’s disease
- Longitudinally studied cohorts of patients with neurodegeneration and dementia, well characterised with structural and functional brain imaging and cognitive biomarkers
- Generational study of people aged 65 and over with 2,500 characterised population sample locally and 7,500 in total in three sites in England and two further sites in Wales
- Parkinson’s Disease, including long term tracking of cognition and clinical course, aged matched control cohorts.
NIHR Dementia Biomedical Research Unit
The NIHR Cambridge Dementia Biomedical Research Unit (BRU) brings together world-leading pipelines for preclinical and clinical discoveries relevant to dementia. The Unit combines a group of internationally-recognised researchers harnessing a rich inter-disciplinary interface to solve problems impeding effective classification and treatment of dementia. The Director of the NIHR Cambridge Dementia BRU is Professor Peter St George-Hyslop.

NIHR Biomedical Research Centre
The NIHR Cambridge Biomedical Research Centre (BRC) has research themes focusing on dementia and neurodegeneration. Dr John Bradley is the BRC Director and the Dementia and Neurodegeneration research theme is led by Professor Roger Barker.

Key features:
- Application of advanced technologies for screening of candidate therapies. These include the use of induced neurons from skin fibroblasts of carriers of disease-causing alleles of genes associated with dementia
- Application of molecular neuroimaging and advanced MRI and PET imaging methods including ligand development for inflammation and tau deposits
- Advanced cognitive neuroscience for the design of novel tests for cognitive impairment
- Expertise in characterising cognitive deficits in terms of intermediate phenotypes that support translation between animal model systems and clinical populations
- Expertise in the epidemiology of dementia in the community and the implications of new findings for public health
- Detailed understanding of autophagy in relation to neurodegeneration
- Based at the Wolfson Brain Imaging Centre, neuroimaging capabilities using PET and 3T MRI embedded in a clinical environment, with the facility to study critically ill and challenging patients
- The development and validation of novel imaging technologies including radiopharmaceuticals for PET, amyloid plaque imaging
- The identification of novel genes associated with dementia.
NIHR Dementia Biomedical Research Unit

The NIHR Maudsley Dementia Biomedical Research Unit (BRU) accelerates the translation of dementia research from basic science to early phase clinical trials. The Unit focuses on the three common late-onset dementias - Alzheimer’s, Vascular and Lewy body dementia and on Frontotemporal Dementia with Motor Neuron Disease. The Unit provides the link between the Medical Research Council Centre for Neurodegeneration Research at King’s College London and the applied clinical neurosciences at King’s Health Partners. Professor Simon Lovestone is the Director of the BRU.

NIHR Biomedical Research Centre

The NIHR Maudsley Biomedical Research Centre (BRC) focuses on four main areas: early detection and intervention of psychiatric disorders; personalisation of treatments based on genomics, biomarkers and psychological traits; experimental medicine to provide proof-of-concept for innovative medical and psychological treatments; and exploring the mental-physical health interface for more effective treatments. Professor Simon Lovestone is the Director of the NIHR Maudsley Biomedical Research Centre.

Key features:

- Experimental Medicine studies utilising imaging and biomarkers
- Discovery, validation and qualification of biomarkers using genomics and proteomics
- MRI and PET neuroimaging; development and validation of new methodologies and utilisation in clinical trials and related research
- Electronic Medical Records with appropriate safeguards for consent and confidentiality for use in research for: care pathway mapping, for risk evaluation and aides to decision making, for trials feasibility studies and for recruitment to clinical research including interventional trials
- A developing programme in research on patients using neurons derived from Induced Pluripotent Stem Cells including biomarker and drug discovery related studies
- Bioinformatics and Biostatistics – which includes the use of electronic medical records for research and developing linkages between patient data and large variable biological datasets
- Development and implementation of neuroimaging (MRI, PET and EEG) for better diagnosis, improved understanding of disease biology, enhanced prediction of response heterogeneity and clearer patient stratification for both translational and clinical studies.
NIHR Dementia Biomedical Research Unit

The NIHR Newcastle Dementia Biomedical Research Unit (BRU) focuses on Lewy body dementia, including Parkinson’s Disease patients who later develop dementia. Newcastle is a recognised world-leader in research into Lewy body dementias. These complex and disabling conditions affect around 160,000 older people in the UK. They are the most common form of dementia after Alzheimer’s Disease. The Director of the NIHR Newcastle Dementia Biomedical Research Unit is Professor David Burn.

NIHR Biomedical Research Centre

The NIHR Newcastle Biomedical Research Centre (BRC) focuses on the complex healthcare needs of the older person, based on an advanced understanding of the ageing process and age-related disease and aims to deliver personalised medicine for the older patient. Professor Patrick Chinnery is the Director of the BRC and Professor Ian McKeith is the Ageing Brain research theme lead.

Key features:
- Well characterised cohorts of Parkinson’s and Lewy body dementia subjects with deep phenotyping information available for many
- Novel biomarker approaches, including gait metrics and activity monitoring, supported by a gait laboratory with a state-of-the-art Vicon camera system and GaitRite mat
- High quality clinical trial facilities for translational medicine studies located on a Campus designed for the older person
- Strong international links with other Lewy body researchers, and a leading role in influencing management and therapeutic guidelines in the Lewy body dementias
- World class underpinning basic science on underlying mechanisms of ageing with relevance to neurodegenerative disease
- Leading international contributions to clinical diagnosis, nosology, diagnostic criteria and therapeutics
- A well-established international track-record in the pathophysiology and treatment of dementia with particular strengths in the non-Alzheimer types. In addition to the Lewy body dementias, Newcastle also has research strengths in vascular dementia
- Recognised expertise in systems biology, aging, frailty and chronic disease.
NIHR Dementia Biomedical Research Unit

The NIHR Queen Square Dementia Biomedical Research Unit (BRU) has a focus on Young-Onset Dementias and the development of new methods of diagnosis and treatment. These and other degenerative dementias often occur on an autosomal dominant inherited basis, with the same clinical features as sporadic disease. Identification of the mutated genes causing the dementia, and longitudinal study of individuals who carry the gene, create a window on the disease process. Professor Martin Rossor is the Director of the BRU.

NIHR Biomedical Research Centre

The NIHR University College London Hospitals Biomedical Research Centre (BRC) has research themes in neurodegeneration, neuroimaging and neurodiagnostics which have a focus on dementia. These themes are led by Professors John Collinge, Tarek Yousry and John Duncan respectively.

Key features:

- Diagnostic MRI
- Image analysis of serial brain MRI data, with techniques that offer automated measures of tissue and organ volumes and precise quantification of rates of loss in, for example, whole brain hippocampus and other tissues
- Analysis of Cerebro Spinal Fluid (CSF)-based tau, phospho-tau and Abeta markers
- Developing novel CSF markers
- Expertise in induced pluripotent stem cell derived neurons
- Neuroimaging - UCLH and UCL lead the field of Neuromaging (NI) research topping a recent national survey with 30 percent of the total high quality publications
- Comprehensive characterisation of patients with, or at high risk of developing, neurodegenerative disease and definition of patient cohorts
- Understanding prion neurodegeneration, which is considered a prototypic protein misfolding disease. It can be used to understand the common mechanisms and interactions between different neurodegenerative diseases, which also involve accumulation and anatomical spread of misfolded proteins
- Use of bioinformatics to interpret large amounts of genetic data in large cohorts to develop meaningful biomarkers.
NIHR Biomedical Research Centre

The NIHR Imperial Biomedical Research Centre (BRC) has access to well-characterised patients through the Academic Health Science Centre of five merged hospitals, which serves a population of 2.8 million across West London.

Professor Jonathan Weber is the Director of the NIHR Imperial Biomedical Research Centre. Professor David Brooks leads the Neuroscience research theme which focuses on neurodegeneration, traumatic brain injury and stroke. This research theme is also closely linked to the Imaging cross-cutting theme, which Professor Eric Aboagye leads.

Key features:

- **Neuroimaging** – Imperial hosts Imanova, a pan-London Positron Emission Tomography (PET) and Magnetic Resonance Imaging (MRI) company jointly owned by Imperial College, University College, and King's College London Universities and the Medical Research Council. Imperial currently run programmes on in vivo amyloid imaging and detection of inflammation in dementia and patients with mild cognitive impairment. It participates in trials of anti-amyloid strategies such as the recent Bapineuzimab and Gantenerumab immunotherapy trials. Imperial are also exploring the relationship between the presence of amyloid pathology and both late onset depression and delirium.

- **Clinical Trials Unit** with records of over 1000 cases of dementia and mild cognitive impairment in the NW Thames area. The unit is actively running therapeutic trials of novel symptomatic and putative neuroprotective agents.

- **Biomarker discovery and its influence on disease progression**

- **Measuring systemic levels of inflammatory biomarkers in neurodegenerative disorders and correlating these with in vivo imaging findings.** Imperial were a part of the consortium responsible for identifying the role of the FUS gene in frontotemporal dementia and amyotrophic lateral sclerosis (ALS).

- **Genetics of vascular disease and Amyotrophic lateral sclerosis**

- **Active genetics programmes designed to validate systemic diagnostic biomarkers for stroke and for characterising subtypes of ALS**

- **UK Parkinson's and Multiple Sclerosis Brain Bank.** The aetiologies of dementia in Parkinson's disease and the association of previous brain trauma in dementing disorders are being actively researched.
The NIHR Oxford Biomedical Research Centre (BRC) focuses on multidisciplinary translational research for patients with dementia and on the development and application of interventions to promote healthy ageing. Professor Keith Channon is the Director of the NIHR Oxford BRC. Dementia-related research activities are distributed among Oxford BRC’s Dementia & Cardiovascular Disease Theme (led by Professor Peter Rothwell and Dr Sarah Pendlebury), Functional Neuroscience & Neuroimaging Theme (led by Professor Peter Brown), and Cognitive Health Programme (led by Professors Kia Nobre and Heidi Johansen-Berg).

**Key features:**
- Epidemiological, clinical, neuropsychological, and neuropharmacological assessment of cognition in aging and dementia
- Multimodal structural and functional brain imaging and analysis, particularly magnetic-resonance imaging and magnetoencephalography
- Patient-derived induced pluripotent stem cell (iPSC) neuronal models of neurodegenerative disease for drug discovery
- Genomics platforms, neuroimaging, and the application of state-of-the-art gene-sequencing and expression technologies to understand disease pathways, clinical diagnosis, and disease stratification
- Improve identification and develop cohorts of presymptomatic individuals at-risk of Vascular Dementia (VaD), Parkinson’s Disease (PD), or Dementia with Lewy Body (DLB)
- Establish large, highly-phenotyped cohorts of healthy aging individuals and early-stage PD for multidisciplinary studies in biomarker discovery, genetics, imaging, proteomics, and stem-cell models of disease
- Determine how expression of genes associated with dementia correlates with degenerative and vascular disease burden in healthy and diseased brains
- Develop and validate blood and CSF biomarkers for VaD and PD
- Develop and implement multimodal imaging and image-analysis methods for improved neural phenotyping and stratification
- Characterise how protective and risk factors interact in aging to affect neuroimaging biomarkers, cognition, and mood
- Test pragmatic interventions to improve prevention of VaD and determine the role of secondary vascular insults leading to step-wise or accelerated progression of dementia
- Determine the effects of physical exercise and cognitive training on enhancing neural plasticity and cognitive health in ageing.
Examples of NIHR Dementia Translational Research Collaboration

First-in-Man Gene Therapy Trial for Parkinson’s Disease in Collaboration with Oxford Biomedica

Investigators in the Dementia and Neurodegeneration theme from the NIHR Cambridge Biomedical Research Centre have conducted a first-in-man gene therapy trial for Parkinson’s disease. The trial used the tricistronic vector developed by Oxford Biomedica to deliver the synthetic enzymes for dopamine (Prosavin) into the brain of patients with this condition. The trial started in Paris with six patients but now involves Cambridge as a second site. The treatment is designed to allow for the better delivery of dopamine within the brain and by so doing smooth out the motor fluctuations of patients with advancing Parkinson’s disease.

Advances in Cell Therapy for Huntington’s Disease

The lack of treatments for Huntington’s disease has led to efforts to pull through advances in cell therapy into the clinic to establish disease modifying treatments. A safety study involving unilateral transplantation of human fetal striatal tissue into the striatum of four patients with Huntington’s disease has demonstrated that the procedure is safe and feasible. Stereotaxic tissue placement following preoperative magnetic resonance imaging was performed in Cambridge by investigators from the NIHR Cambridge Biomedical Research Centre, and Cambridge based protocols for the screening of human fetal tissue for potential pathogens have been developed, with clinical trials underway.

Role of Vascular Factors in Dementia

Pioneering work in Newcastle has defined the importance of vascular factors in both vascular and other dementias, and has had a major impact in terms of revising diagnostic criteria. The work has informed public health campaigns highlighting vascular risk for dementia, such as the Alzheimer’s Society Hearts and Brains initiative. Through collaborative studies, the NIHR Newcastle Biomedical Research Centre has demonstrated the clinical significance of white matter lesions (Inzitari, BMJ 2009), and demonstrated the feasibility of vascular interventions to show their decline (Firbank, J Neurol 2007). These lesions are now a target for future studies.

Automated MRI for Diagnosis of Alzheimer’s Disease

Working with collaborators from the Karolinska Institute, Professor Simon Lovestone and Dr Andy Simmons from the NIHR Maudsley Biomedical Research Centre developed novel multivariate techniques for classifying routine brain images as an aid to early diagnosis of Alzheimer’s disease. The technique demonstrated improved accuracy (Westman J Alz Dis 2010, Neuroimage 2011) and these findings were replicated in a large independent cohort (Westman et al Neuroimage 2011) and demonstrated that it outperformed skilled radiologists (Westman PloS One 2011).

What to do next?

NOCRI connects the country’s expert investigators, technologies and research facilities to deliver world-class clinical research. If you would like to know more about how NOCRI can help you to establish academic-NHS-industry collaborations, please contact nocri@nihr.ac.uk
NOCRI provides a single and consistent point of contact for industry to access the world-leading expertise within the National Institute for Health Research Dementia Translational Research Collaboration, which was launched as part of the Prime Minister’s Challenge on Dementia. NOCRI facilitates early phase collaboration and provides the tools to support successful interactions between industry and the NIHR Dementia Translational Research Collaboration and can help shorten the contracting process for collaborative relationships.

Mark Samuels
Managing Director, NOCRI

For further information or support with research collaborations, contact: nocri@nihr.ac.uk

For further information visit:
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